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Parvalbumin as a sex-specific target in Alzheimer's disease research – A mini-review

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ABSTRACT

Alzheimer's disease (AD) is the most common form of dementia, and both the incidence of this disease and its associated cognitive decline disproportionally effect women. While the etiology of AD is unknown, recent work has demonstrated that the balance of excitatory and inhibitory activity across the brain may serve as a strong predictor of cognitive impairments in AD. Across the cortex, the most prominent source of inhibitory signalling is from a class of parvalbumin-expressing interneurons (PV^+). In this mini-review, the impacts of sex- and age-related factors on the function of PV^+ neurons are examined within the context of vulnerability to AD pathology. These primary factors of influence include changes in brain metabolism, circulating sex hormone levels, and inflammatory response. In addition to positing the increased vulnerability of PV^+ neurons to dysfunction in AD, this mini-review highlights the critical importance of presenting sex stratified data in the study of AD.

1. Sex differences in Alzheimer's disease onset and progression

Alzheimer's disease (AD) is a progressive neurodegenerative disease characterized by impaired cognitive function. AD is the most common form of dementia, affecting approximately 1 in every 9 individuals over the age of 65 in North America (Rajan et al., 2021). With an aging global population in which an increased proportion of the population is reaching 65 years of age and older, it is projected that by 2050 the total number of individuals affected by AD will double (Hebert et al., 2001). This projection paints a troubling image given the lack of cure and limited treatment options currently available for affected individuals.

To improve treatment, it is critical to deepen understanding of disease progression and etiology. Approximately 1% of AD cases have been linked to deterministic familial gene mutations, which lead to early onset AD (i.e. prior to age 65) (Harvey et al., 2003). These mutations in the amyloid precursor protein (APP), presenilin-1 (PSEN1) and presenilin-2 (PSEN2) genes have been linked to an increased accumulation of amyloid plaques alongside of impaired cognitive function. However, the vast majority of AD cases are considered to be largely sporadic. Although, there are genetic risk factors, the most prominent being the APOE-e4 gene, these tend to interact with other risk factors, and in many cases the cause of the disease is unknown. Despite the differences in etiology between familial and sporadic AD, there are similarities in the amyloid neuropathology. This association has led some to infer a causative relationship between the accumulation of amyloid plaques and the development of AD (Hardy and Selkoe, 2002; Masters et al., 2006). This inference hinges on impaired clearance of amyloid-β, a by-product of the proteolytic cleavage of the amyloid precursor protein by β-secretase. With impaired clearance of this toxic by-product, soluble forms of oligomeric amyloid-β interact with microglia, astrocytes, and neurons to induce various cellular responses which ultimately contribute to neuron death (Allaman et al., 2010; d'Errico et al., 2022; Wirths et al., 2004). This theory, termed the "amyloid hypothesis" inspired years of basic science research and eventual clinical trials examining the effects of amyloid clearance in patients with AD (Karran and De Strooper, 2022). While pharmacological innovations have led to the ability to effectively clear amyloid plaque accumulation from the brains of clinical trial participants suffering from AD, measures of recovery or preservation of cognitive function have proven to be minimal at best (Salloway et al., 2014; van Dyck et al., 2023).

While amyloid pathology is widely present in the AD brain and increases over the course of disease progression, there is evidence that the amount of amyloid pathology does not necessarily correlate well with the severity of cognitive impairments. Similarly, the reduction of amyloid does not appear to substantially improve cognition (Ackley et al., 2021; Aizenstein et al., 2008). While other pathological markers, such as

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increased tau burden through the accumulation of neurofibrillary tangles, has often been reported as being marginally more predictive of cognitive outcomes than amyloid accumulation, their predictive power is still relatively weak (Guillozet et al., 2003; Hanseeuw et al., 2019). Factors have since emerged which seem to have much better predictive power over the extent of cognitive decline in AD, such as altered balance of excitatory and inhibitory signalling (Aguiar-Furucho and Peláez, 2020; Bai et al., 2015; Jiménez-Balado and Eich, 2021). Similar studies have also proposed that the ability of this marker to predict cognitive outcomes in AD is sex dependent, wherein they better predict outcomes in women (Alia and Roßner, 2018). This is of particular interest, as the risk of developing AD is twice as high in women than in men, even after accounting for the shorter average lifespan reported in men (Andersen et al., 1999; Chêne et al., 2015; Gao et al., 1998).

The increased risk of developing AD among women is further complicated by differences in rates of cognitive decline and in the efficacy of currently available treatments. Sex differences in the rates of progression have been consistently reported among individuals with mild cognitive impairment (MCI), wherein cognitive deterioration is faster in women than in men (Buckley et al., 2020; Holland et al., 2013; Levine et al., 2021; Lin et al., 2015; Mielke et al., 2014). However, when only considering advanced stages of AD, it has been shown that the relative rates of cognitive decline shift towards being faster in men (McCarrey et al., 2016). These studies have suggested that while cognitive impairment generally hits more dramatically in men during advanced stages of AD, the impacts of cognitive decline can often be detected much earlier in women. This earlier detection of relative cognitive decline coincides with earlier emergence of AD-related changes in the brain, suggesting an earlier onset of AD in women (Mosconi et al., 2018, 2017b). At face value, this suggestion may seem contradictory to clinical reports, which often show an earlier onset of overall cognitive impairment in men (Hale et al., 2020). However, it has been suggested that higher baseline performance in healthy women across many cognitive tests used to assess mild cognitive impairment may mask the extent of cognitive impairment in women, as a greater relative decline in cognitive performance is required to reach diagnostic criteria, potentially contributing to a later age of diagnosis (Castro-Aldrete et al., 2023; Sundermann et al., 2021).

When considering the efficacy of currently available treatments for AD, there is much debate as to whether sex effects exist in these data (Greenberg et al., 2000; Haywood and Mukaetova-Ladinska, 2006; Lawlor et al., 2018; Saif et al., 2022; Winblad et al., 2001). In 2017, Canevelli et al. conducted a systematic review of randomized controlled studies which applied either of the two most widely marketed treatments of AD at the time: cholinesterase inhibitors and memantine. Their meta-analysis revealed that while they were unable to identify significant differences in treatment efficacy of these compounds between men and women, only two of the 48 studies which met their criteria considered sex as a variable during their analyses (Canevelli et al., 2017). Additionally, in this meta-analysis none of the randomized control studies considered the potential for sex differences in the safety or tolerability of these treatments (Canevelli et al., 2017). In an even more recent meta-analysis of published randomized clinical trials, Martinkova et al. demonstrated that little has changed in the approach to these analyses. While they reported that approximately half of the studies meeting their inclusion criteria included sex as a variable in their randomization schemas, only 12.5% of the publications reported sex-stratified results (Martinkova et al., 2021).

While these data suggest a temporal trend towards increased reporting of sex-stratified data, it paints a bleak picture when considering our current limited understanding of AD and the sex differences in its epidemiology. Therefore, it is critical to expand our understanding of not only factors which are predictive of the development of AD pathology, but also sex-specific vulnerabilities and differences in epidemiology.

2. Inhibitory balance in Alzheimer's disease

Recent work has demonstrated that the balance of excitatory and inhibitory factors across the brain may serve as a strong predictor of cognitive impairments (Murari et al., 2020). In these cases, participants with MCI or AD showed decreased GABA levels in the prefrontal cortex, which also positively correlated with impaired long-delayed verbal memory and immediate nonverbal memory (Murari et al., 2020). GABA is the primary inhibitory neurotransmitter in the brain, binding to ionotropic or metabotropic receptors on postsynaptic neurons to inhibit their function (Govindpani et al., 2017). In several brain regions, there is evidence of reduced GABA in AD, as well as evidence suggesting relationships between GABA levels and cognitive performance even in healthy aging (Bai et al., 2015; Gueli and Taibi, 2013; Porges et al., 2017).

The relationship between GABA and cognitive performance can be understood as a shift in the balance of excitatory and inhibitory neuronal connections (E/I balance). Neuronal communication in a healthy brain requires a well-regulated E/I balance, which enables the temporal synchronization of neuronal activity to generate distinct firing patterns (Buzsáki, 2015; Hu et al., 2013; Schönberger et al., 2014). These patterns, such as gamma oscillations, are rhythmic fluctuations in the activity of local neuron populations which serve important functions in the maintenance of cognitive function (Fujisawa and Buzsáki, 2011; Montgomery and Buzsáki, 2007). Synchronicity is also important from the perspective of maintaining patterns of coactivation between sets of neuroanatomical regions across the brain. In this sense, synchronization allows groups of regions to communicate effectively as functionally connected networks (Hampson et al., 2002). A classic example of network synchrony is the default mode network, which is a group of neuroanatomical regions which synchronize to become coactive during periods of rest and self-reflection (Fox et al., 2005; Raichle et al., 2001). In AD, the coordinated activity of the regions in the default mode network has been shown to be perturbed, with distinct alterations to E/I balance in these regions (Caldwell et al., 2019; Greicius et al., 2004). Equally important to the ability to generate these synchronized activity patterns is the ability to suppress firing and avoid hypersynchrony (Ranasinghe et al., 2020; Targa Dias Anastacio et al., 2022). Tissue samples collected from individuals with AD have demonstrated that this condition is marked by an increased excitatory to inhibitory synaptic ratio, thereby increasing the potential for neuronal activity to be pushed towards a state of hypersynchrony (Lauterborn et al., 2021).

Altered E/I balance and the resulting issues of hyperexcitability and hypersynchrony have consequences for cognitive capacity. In humans, it has been demonstrated that slight natural fluctuations in this balance may facilitate memory retrieval; however, sustained deviations lead to impaired cognitive functions (Bookheimer et al., 2000; Filippini et al., 2009; Koolschijn et al., 2021). Notably, the deviations in network activity resulting from GABAergic dysfunction can even be detected prior to AD diagnosis and are able to moderately predict future pathology (Aguiar-Furucho and Peláez, 2020; Corriveau-Lecavalier et al., 2023; Jiménez-Balado and Eich, 2021; Mondadori et al., 2006). Therefore, it is critical to improve our understanding of the shift in E/I balance and loss of GABAergic transmission which occurs in AD.

3. Parvalbumin: inhibitory control with sex-specific vulnerability

The E/I balance of the brain is mediated by the activity of GABAergic interneuron populations, which can be divided into 5 main molecular classes: parvalbumin-expressing (PV^+), somatostatin-expressing, neuropeptide Y-expressing, vasoactive intestinal peptide-expressing, and cholecystokinin-expressing. The most abundant class of interneurons in the cortex is PV^+ neurons, with roughly 50% of the interneurons in these regions expressing this protein (McDonald and Betette, 2001; Tamamaki et al., 2003). PV^+ neurons are characterized by their fast steady-state

firing rate (Kawaguchi and Kubota, 1997). Synapsing onto hundreds of cells at once, PV^+ neurons regulate the synchronization of principal neurons through inhibitory GABAergic innervation (Bartholome et al., 2020). These properties make them potent regulators of neuronal circuits, critical for maintaining proper E/I balance and regulating the functional connectivity of large brain networks. Due to their elevated firing rate and vast connectivity, these cells require considerably more metabolic resources to maintain their steady-state firing rate than principal cells (Kann et al., 2014, 2011). Consequently, PV^+ neurons are particularly vulnerable to changes in metabolism, and impaired activity of these neurons in metabolic dysfunction has been associated with cognitive impairments across a variety of conditions, such as schizophrenia, autism spectrum disorders, and Alzheimer's disease (Chao et al., 2010; Shu et al., 2023; Tomasella et al., 2020).

Analyses of post-mortem tissues have yielded contradictory results about the presence of impaired PV^+ neurons in AD, with some studies showing no differences in their expression density in the brains of patients with AD and control patients (Hof et al., 1991; Sampson et al., 1997) and others demonstrating disrupted expression of these cells in AD (Sanchez-Mejias et al., 2020; Solodkin et al., 1996). When interpreting these results and attempting to understand this variability, it is important to consider the potential for sex differences in the vulnerability of PV^+ neurons. None of these prior studies were designed to investigate sex differences, with limited group sizes and no mention of sex anywhere in these manuscripts. With a cellular target such as PV^+ neurons, which have ample potential for sex-specific vulnerabilities which will be presented below, differences in the ratios of males and females within experimental groups can have serious repercussions on the results of these studies.

Additionally, it has been noted that not all brain regions are equally susceptible to AD pathology, with the onset of pathology varying from region to region. In terms of the accumulation of amyloid plaques, the development of this pathology has been observed to occur earlier in the medial orbitofrontal and posterior cingulate cortices than in the striatum (Grothe et al., 2017; Palmqvist et al., 2017). It is expected that the degree of PV^+ neuron impairment may also differ regionally, yet also be related to disease progression (Sanchez-Mejias et al., 2020). For example, studies have noted impaired PV expression in the medial temporal cortex in samples from patients who had suspected AD for approximately 5.5 years; however, at a similar stage of disease progression, no change was reported in the density of PV^+ neuron expression in the parietal cortex (Inaguma et al., 1992; Solodkin et al., 1996). In more advanced cases of AD, with tissue samples obtained from patients who had suspected AD for approximately 15 years, impaired expression of PV^+ neurons was observed in the temporal and parietal cortices (Satoh et al., 1991).

3.1. Metabolic requirements

The high energetic requirement of PV^+ neurons is maintained by a high density of mitochondria (Gulyás et al., 2006). With high mitochondrial density comes a high density of cytochrome *c* oxidase (an enzyme necessary for ATP synthesis) to support these bioenergetic demands. However, heightened cytosolic cytochrome *c* release has been linked to apoptosis, thus suggesting that while PV^+ neurons have the capacity to fire at high rates, they are particularly vulnerable to disrupted metabolic activity (Liu et al., 1996; Whittaker et al., 2011). Therefore, it is not surprising that glucose hypometabolism, an early marker of AD pathology, has detrimental influence over the maintenance of PV^+ neurons (Mosconi et al., 2008; Povysheva et al., 2019).

Brain metabolism changes across neuroendocrine transition states During perimenopause, the brain enters a hypermetabolic phase in which subsets of neurons exhibit increased bioenergetics through the up-regulation of oxidative phosphorylation (Hirai et al., 2001; Zhu et al., 2006). Given their reliance on oxidative phosphorylation, the subset of neurons which are driving this hypermetabolic state generate more reactive oxygen species (Behrens and Sejnowski, 2009). This increase in reactive oxygen species progressively increases oxidative damage to the brain during this period, further contributing to neurodegeneration (Behrens and Sejnowski, 2009). During the subsequent postmenopausal period, brain glucose metabolism gradually decreases, further increasing the risk of metabolic disruption in the brain as energetic resources become more scarce (Mosconi et al., 2017a; Schönknecht et al., 2003). In studies of cognitively healthy individuals, it was shown that menopausal status was the main predictor of brain metabolism in women (Rahman et al., 2020).

Age-related changes in brain metabolism are not exclusive to women. Under healthy aging conditions, the male brain also displays glucose hypometabolism (Gaignard et al., 2017). However, the decrease in metabolism observed in the male brain occurs considerably more gradually with age than it does in women (Ernst et al., 1998; Kakimoto et al., 2016). In AD, there are sex differences in the progression of brain hypometabolism. A recent study used fluorodeoxyglucose-PET (FDG-PET) to assess changes in brain glucose metabolism over a two-year period (Park et al., 2023). Here, women with AD showed the greatest reduction in FDG-PET at the follow-up timepoint. Given the high metabolic requirements of PV^+ neurons, it is reasonable to predict that these cells may have a critical metabolic threshold. This prediction, along with lower basal metabolic rate in females during aging, and an exacerbated rate of hypometabolism in females in AD, would then also suggest that this cell type may be more vulnerable to perturbation in women than in men.

3.2. Influence of sex hormones

The depletion of sex hormones is a normal consequence of aging and is often associated with increased vulnerability to disease in hormone-responsive tissues like the brain (Fillit and Luine, 1997; Morley, 2001). Following menopause, the production of estradiol and progesterone decreases rapidly in women. In men, an age-related decrease occurs in terms of testosterone circulation, however, this decrease is much more gradual than the decrease in estradiol and progesterone production which occurs in women.

In men and women, the age-related depletion of sex hormones is linked to an increased risk of AD. Multiple studies have examined the relationships between low levels of circulating sex hormones and the incidence of AD in both men and women and have provided support that in age-matched controls, low levels of sex hormones serve as a good predictor of AD in age-matched comparisons (Manly et al., 2000; Paoletti et al., 2004). One theory supporting these observations, the gonadotropin hypothesis, arose from findings that low levels of circulating estrogens and androgens lead to elevated levels of luteinizing hormone (LH) (reviewed in Gregory et al., 2006). In animal models, overexpression of LH on its own disrupts cognitive performance in otherwise normal and healthy mice (Casadesus et al., 2007). Conversely, decreasing LH through administration of the gonadotropin releasing hormone agonist leuprolide acetate improves cognitive performance in mouse models of AD (Casadesus et al., 2006). Additionally, sex hormones have also been shown to influence the relationship between brain-derived neurotrophic factor (BDNF) and tyrosine receptor kinase B (TrkB). The maturation of PV^+ neurons requires the binding of BDNF to TrkB receptors on the surface of these cells, which stimulates a further cascade on intracellular signalling pathways (Guyon et al., 2021; Lau et al., 2022). Across many brain regions, increased circulating estradiol levels are associated with increased expression of BDNF and TrkB phosphorylation (Gibbs, 1999; Liu et al., 2001; Sohrabji et al., 1995; Solum and Handa, 2002). In males specifically, gonadectomy-induced testosterone depletion reduces the expression of BDNF; however, classical TrkB signalling can be restored with testosterone replacement (Purves-Tyson et al., 2015). Together, these mechanisms highlight several indirect means through which age-related decreases in circulating sex hormones can influence the vulnerability of PV^+ neurons.

Longitudinal studies of the relationship between sex hormone levels and the incidence of AD have provided evidence that this decrease in sex hormones precedes the onset of AD symptoms (Chu et al., 2010; Rosario et al., 2010). Furthermore, pharmacological manipulation of circulating sex hormone levels have been shown to influence susceptibility to cognitive decline in AD. Considering androgen deprivation therapy in the treatment of prostate cancer, exposure to this therapy has been associated with subsequent brain hypometabolism and diagnosis of AD or dementia (Cherrier et al., 2018; Jayadevappa et al., 2019). Conversely, the use of hormone replacement therapy in postmenopausal women has been shown to be protective against impairments to brain metabolism and is associated with reduced risk of subsequent development of AD (Coughlan et al., 2022; Saleh et al., 2023; Silverman et al., 2011). These results have led to speculation that rather than a consequence of AD, decreased sex hormone circulation may be a contributing factor to the development of AD.

Previously, we outlined the influence of declining sex hormone circulation on metabolism as an indirect influence on the activity of PV^+ neurons. Estradiol and testosterone also have the potential to influence PV^+ neurons directly. In women, it is important to note that PV^+ neurons contain high densities of β-type estrogen receptors and are directly affected by changes in estradiol levels with age (Blurton-Jones and Tuszynski, 2002; Ferando and Mody, 2013; Gilfarb and Leuner, 2022; Wu et al., 2014). These receptors increase the excitability of these fast-spiking interneurons, thus increasing their ability to regulate regional neuronal activity (Clemens et al., 2019). This is further supported by evidence that treatment with estradiol and selective estrogen receptor modulators, such as raloxifene, has been shown to recover gamma oscillations (Schroeder et al., 2019). Therefore, it is reasonable to conclude that decreased estradiol after menopause contributes to decreased activity of PV^+ neurons.

In men the influence of sex hormones on these neurons is also quite nuanced. In the brain, testosterone can both act on androgen receptors directly or be converted into estrogens, primarily estradiol via aromatase (Naftolin and Ryan, 1975). As such, it is possible many of the changes attributed to decreased circulating testosterone involve similar mechanisms as those which are vulnerable to decreased estradiol. However, there are consequences of decreased testosterone which are presumed to be mediated by its activity on androgen receptors, as they have not been described with decreased circulating estradiol alone. One such effect is that testosterone has been shown to stimulate the development of perineuronal nets (PNNs) around PV^+ neurons, which may have protective effects shielding the connectivity of these cells (Cornez et al., 2020). PNNs are structures in the extracellular matrix which, throughout many cortical regions, primarily surround PV^+ neurons. Their mesh-like structure regulates the plasticity of PV^+ neurons, as contacts onto these cells are restricted by the contiguity of the PNNs (Corvetti and Rossi, 2005). As a result of this regulation of PV^+ neurons, dysregulated expression of PNNs can have considerable consequences on E/I balance in the brain (Gottschling et al., 2019). Particularly in the case of AD, impaired PNN expression has been observed in the frontal cortex and middle frontal gyrus, though the potential influence of sex on this disturbance was not considered (Baig et al., 2006; Crapser et al., 2020). Furthermore, testosterone both induces the release of anti-inflammatory cytokines and represses the release of pro-inflammatory cytokines, thereby protecting PV^+ neurons from possible damage from inflammation (Zhang and Reynolds, 2002).

3.3. Influence of inflammation

Sustained inflammatory response is often considered a core feature of AD pathology (Cribbs et al., 2012; Lagarde et al., 2018; Sudduth et al., 2013). In the brain, inflammation is a double-edged sword, serving a neuroprotective role during an acute-phase response, but detrimental consequences emerge during periods of chronic inflammation (Kim and Joh, 2006). During these periods of chronic inflammation, proinflammatory cytokines have been shown to exacerbate amyloid burden (Goldgaber et al., 1989). As such, some now believe that the neuroinflammation observed in AD plays a fundamental role in the progression of the neuropathological changes which are observed in AD (Kinney et al., 2018).

Multiple lines of evidence suggest differences in both innate and adaptive immune response between men and women (Jaillon et al., 2019; Klein and Flanagan, 2016; Tronson and Collette, 2017). In the central nervous system, it has been noted that during acute neuroinflammation, adult male mice show greater glial activation compared to age-matched female mice (Doran et al., 2019). In this same study, basal levels of the proinflammatory cytokine interleukin-1β (IL-1β) were higher in female mice relative to age-matched male mice, a result which coincides with the findings of a large population-based study conducted in Switzerland (Marques-Vidal et al., 2011). In mice, IL-1β levels remain relatively stable across both male and female control groups during healthy aging; however, in 5xFAD mice – a transgenic mouse model of AD – the expression of IL-1β increases with age in females, while this factor shows no statistical significance in males (Manji et al., 2019). These differences in circulating IL-1β could contribute to the greater immune activities from myeloid cell populations in females than in males (Sheridan and Murphy, 2013).

Due to their high energy demands, PV^+ neurons are particularly susceptible to dysfunction under inflammatory conditions. With acute inflammation, the activity of PV^+ neurons increases and the miniature inhibitory postsynaptic currents of pyramidal neurons becomes more frequent, shifting the synaptic balance towards heightened inhibition (Feng et al., 2021; Tang et al., 2020). When neuroinflammation extends from an acute phase to a chronic phase, the opposite effects are shown on the density of PV^+ neuron expression and the synaptic balance of the brain, which then begins to show greater cortical disinhibition (Ji et al., 2020; Yates et al., 2022).

3.4. Histological and electrophysiological consequences

With metabolic, hormonal, and inflammatory influences compounding upon each other, it is not unexpected that the histological presentation and electrophysiological properties of PV^+ neurons are affected by sex and AD pathology. In clinical presentation and animal models of AD, the expression density of PV^+ neurons has been shown to decrease with age (Ali et al., 2019; Cattaud et al., 2018; Saiz-Sanchez et al., 2016; Sanchez-Mejias et al., 2020; Solodkin et al., 1996) in many areas of the brain. While increased amyloid pathology may be associated with decreased density of PV^+ neurons in some regions, notably the entorhinal cortex, it does not seem to predict the loss of PV^+ neurons globally, including in the prelimbic or cingulate cortices (Ali et al., 2019; Solodkin et al., 1996). However, it appears that markers of altered metabolism, sex hormones, and inflammation each seem better suited as predictors of PV^+ neuron loss (Cabungcal et al., 2006; Filice et al., 2018; Ruden et al., 2021; Steullet et al., 2017).

Along with these changes in the density of PV^+ neuron expression, there are several electrophysiological properties which point to impaired function of these neurons in AD. Animals models of AD often display reduced inhibition on principal excitatory neurons in the hippocampus and some cortical regions, such as the parietal cortex, the entorhinal cortex, the prefrontal cortex, and the retrosplenial cortex (Chen et al., 2018; Rey et al., 2022; Ruiter et al., 2020; Shu et al., 2023; Terstege et al., 2023; Verret et al., 2012). This impaired inhibition is often described as decreases in the rate of spontaneous inhibitory postsynaptic currents, their rise rate, and even their amplitude. Examining PV^+ neurons directly in the hippocampus of these models, the spiking activity of these cells is reduced, with this impairment occurring relatively early in the pathological progression of AD (Caccavano et al., 2020). A major consequence of this altered electrophysiological activity of PV^+ neurons and their reduced ability to properly regulate the activity of principal neurons is altered synchronicity of local functional

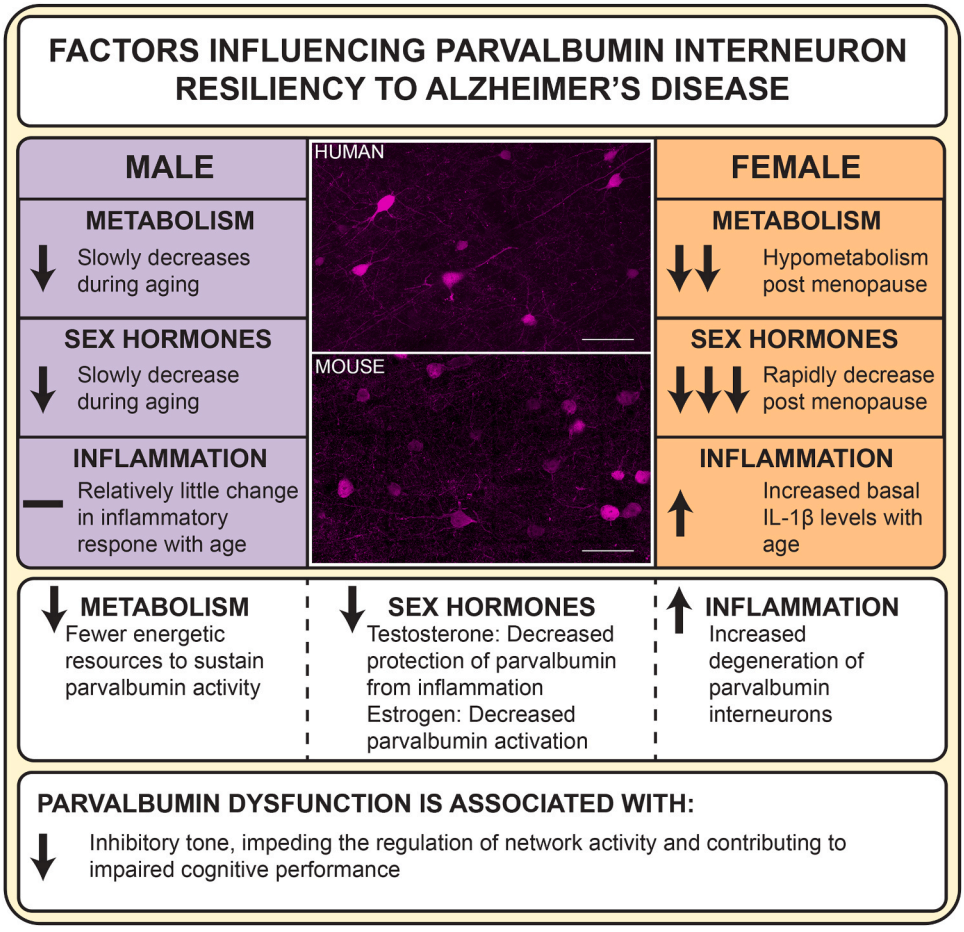

Fig. 1. Summary of findings. Many factors can influence the vulnerability of parvalbumin-expressing interneurons to degeneration in Alzheimer's disease, including changes in metabolism, sex hormones, and inflammatory response. In females, brain hypometabolism, a rapid decrease in circulating estradiol levels, and increased basal IL-1β may all contribute to an age-dependent decrease in the resiliency of parvalbumin interneurons to Alzheimer's disease. Parvalbumin-expressing cells from human (top) and mouse (bottom) were stained with a solution of 1:1000 rabbit anti-parvalbumin (Invitrogen, PA1–933) and 1:500 alpaca anti-rabbit Alexa Fluor 647 (Jackson ImmunoResearch, 611–005–215). Images were captured using an OLYMPUS FV3000 confocal microscope equipped with a 60X objective (N.A. 1.42; 1.9X digital zoom, total magnification: 114X). Scale bar represents 50 μm.

activity networks (van Deursen et al., 2008). Across the hippocampus, mouse models of AD have displayed decreased slow gamma oscillations, decreased fast gamma oscillations, and impaired phase-amplitude coupling for slow gamma oscillations (Etter et al., 2019; Goutagny et al., 2013). These impaired firing properties of PV^+ neurons in the hippocampus have been believed to play a considerable role in cognitive decline, particularly with respect to issues of attentional selection and memory operations (Colgin and Moser, 2010; Knoferle et al., 2014).

Like histological density, the influence of metabolism, sex hormones, and inflammation on the electrophysiological activity of PV^+ neurons has been well documented. Even mild metabolic stress is sufficient to decrease hippocampal gamma oscillatory power in mice (Elzoheiry et al., 2020). Considering sex hormones, increasing the levels of circulating estradiol can increase fast gamma oscillations in the hippocampus of female mice, while reduced gamma oscillations are observed in mouse models of human menopause (Hernández-Vivanco et al., 2022; Vrontou et al., 2022). Chronic inflammation can lead to reduced hippocampal gamma oscillatory activity in otherwise naïve mice, with subsequent treatment of the inflammation being sufficient to partially recover physiological network activity (Gao et al., 2017; Liu et al., 2017).

4. Parvalbumin interneurons as a target for future research

The development of tools for targeting specific cellular populations has opened the door to exciting new possibilities in the realm of targeted therapeutics. With the development of viral promoters that give the ability to specifically manipulate the activity of PV^+ neurons, we can assess the impact of aberrant or altered activity in these systems on cognitive function (Vormstein-Schneider et al., 2020). Using these tools, it has been demonstrated that recovering the activity of PV^+ neurons in vivo can rescue early spatial memory deficits in the APP/PS1 mouse model of AD (Hijazi et al., 2020a). Furthermore, in healthy control mice, it has been demonstrated that chemogenetically enhancing the activity of PV^+ neurons beyond their normal range can render spatial memories more vulnerable to disruption from amyloid-β (Hijazi et al., 2020b). Presumably, a proper balance of PV^+ neuron activity is required, and this range can be established through cell-type specific viral stimulation approaches. Modulating the activity of target cell populations has been shown to alter the survivability and integration of these cells (Cheng et al., 2014; Jung et al., 2019; Nawreen et al., 2020).

While opto- and chemogenetic manipulations provide means for cell-type specific and region-specific manipulations of PV^+ neurons, clinically approved non-invasive stimulation techniques, such as repetitive transcranial mild stimulation (rTMS), may also allow for widespread manipulation of the activity of PV^+ neurons (Funke and Benali, 2011; Moretti et al., 2022). The use of rTMS in the treatment of AD in the clinic has been a question that has gained considerable attention in recent years, and meta-analyses have identified that when it has been applied it has largely been able to improve cognitive function and daily living ability in AD patients (Wei et al., 2022; Weiler et al., 2020). However, these meta-analyses have been hampered by a lack of sex-stratified data presentation, relatively small sample sizes, and short follow-up periods, three important factors when considering the suitability of these approaches as an intervention in AD (Wei et al., 2022).

Another promising avenue of research is the development of preventative measures centered around the promotion and maintenance of PV^+ neurons early in life. Lifestyle-based early intervention strategies are important tools for reducing the prevalence and impact of AD.

There are many early-life factors which can influence the vulnerability and survival of PV^+ neurons in a sex-specific manner later in

adulthood, including exposure to early life stress (Ellis and Honeycutt, 2021; Soares et al., 2020). However, early exposure to environmental enrichment has been shown to promote the survival of PV^+ neurons in adulthood (O'Connor et al., 2019; Urakawa et al., 2013). In clinical studies and using animal models, early life adversity has been associated with the promotion of AD pathology while exposure to cognitive enrichment promotes an increased resiliency to cognitive decline in AD (Donley et al., 2018; Hoeijmakers et al., 2017; Jankowsky et al., 2005; Oveisgharan et al., 2020; Prado Lima et al., 2018; Tanaka et al., 2021). It is possible that, in part, enrichment may promote healthy cognitive aging by preventing the loss of PV^+ neurons.

5. Concluding remarks

As a target cell population whose activity correlates highly with cognitive ability and is particularly vulnerable to many of the documented early markers of AD, PV^+ neurons have the potential to aid in the understanding of sex differences in AD incidence, pathology, and progression. Furthermore, we highlight possible future directions towards the modulation of the activity and preservation of PV^+ neurons in AD as a neuroprotective or neurorestorative measure. Finally, the sex differences in PV^+ vulnerability and function further reinforce the importance of appropriately considering sex and gender variables in the analyses of AD-related data. (Fig. 1).

Author contributions

DJT and JRE conducted the literature review and wrote the manuscript. JRE supervised the project.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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